NCIRS National Centre for Immunisation Research and Surveillance

FactSheet

# Human papillomavirus (HPV) vaccines for Australians

This fact sheet provides information on HPV disease and the available vaccines to assist immunisation providers in the delivery of HPV vaccinations. It can be used in conjunction with the NCIRS resource: HPV vaccines – frequently asked questions, which provides responses to common questions and concerns.

### Disease and epidemiology

- Human papillomavirus (HPV) is a common sexually transmitted infection in both males and females. Most people will acquire an HPV infection within a few years of becoming sexually active.
- A small proportion of HPV infections progress, usually over many years, to cancer. Cancers caused by HPV infection include cervical, vaginal, vulval, penile, anal, and some head and neck cancers.

### Who should be vaccinated

- HPV vaccine is recommended for adolescents aged 12–13 years and is included in the Australian National Immunisation Program (NIP). It is provided via school-based programs for this age group in a two-dose schedule. The second dose is given 6–12 months after the first dose.
- A three-dose schedule is recommended for individuals who commence vaccination at the age of 15 years or older, or for those with significant immunocompromising conditions, with doses given at an interval of 0, 2 and 6 months.
- Those who receive the vaccine before commencing sexual activity will benefit the most from HPV vaccination.
- HPV vaccination is not routinely recommended for adults, but is recommended for men who have sex with men and people with significant immunocompromising conditions, regardless of age.

### Vaccines

- The 9-valent HPV vaccine (9vHPV; Gardasil9), which protects against nine types of HPV, is the vaccine used in the NIP.
- The bivalent HPV vaccine (2vHPV; Cervarix) is available on the private market.
- HPV vaccines are safe and generally well tolerated. The most common side effect is a local reaction at the site of the injection.
- Vaccination does not prevent infection from all HPV types. Therefore, cervical screening remains an important preventive strategy against cervical cancer for women.

# The disease

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses. HPVs infect and replicate within cutaneous and mucosal epithelial tissues. There are 40 known HPV 'types' which infect the mucosal epithelium, classified according to sequence variation in the major genes.

Transmission of genital HPV occurs largely via sexual contact. There is a 50–80% chance of HPV transmission following unprotected sexual intercourse with a person with a current HPV infection.[1-3] The majority of genital HPV infections are subclinical and resolve spontaneously, clearing (i.e. no longer detectable) within 12–24 months of initial infection. Depending on the infecting HPV type, a small proportion of HPV infections can persist (estimated at 3–10%),[4] resulting in cellular abnormalities and, in a subset of cases, precancerous disease; a subset of these progress into cancer. The progression from mucosal HPV infection to cancer can take many years, and not all HPV infections progress to cancer.[5-7]

Of the mucosal HPV types, 13 are designated as 'high-risk' due to their causal association with the development of cervical cancer (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68).[8] These HPV types are also associated with the development of other cancers in females and males, including vaginal, anal and penile cancers, and head and neck cancers. HPV types 16 and 18 are the most common high-risk HPV types found in HPV-positive cervical cancers in Australia[9] and globally, and are the overwhelming cause of all HPV-related cancers.

Of the genital HPV types considered to be 'low risk', types 6 and 11 are major causes of genital warts (causing approximately 95% of genital warts) and recurrent respiratory papillomatosis.[10]

# Epidemiology of HPV infection and associated disease

HPV infection rates vary greatly between geographic regions and population groups. Around 90% of the general population will be infected with HPV at some point in their lives.[11] HPV infection rates among young women are highest soon after they become sexually active.[12] Aboriginal and Torres Strait Islander women have more than twice the risk of developing cervical cancer and a mortality rate four times that of non-Indigenous women.[13,14] However, in men, the risk of acquiring new HPV infection seems to remain stable over time.[15] A person's lifetime number of sex partners is a significant predictor of HPV acquisition, although HPV is frequently acquired from a first and only sexual partner.[16]

The burden of HPV-associated cancers in males in Australia is less than that in women; however, the incidence of HPV-associated anal and tonsillar cancers has been increasing in males in recent decades while remaining relatively stable in females. Men who have sex with men are especially at high risk, with rates of vaccine-type HPV prevalence more than four times that in heterosexual men.[17] The estimated incidence of anal cancer among men who have sex with men in Australia is greater than that of cervical cancer in women prior to the introduction of cervical screening program.[18]

# Who should be vaccinated

## Routine vaccination under the National Immunisation Program

HPV vaccination is recommended for adolescents aged 12–13 years in a two-dose schedule (0, 6–12 months) using the 9vHPV vaccine. Vaccination is mainly delivered through school-based programs, but is available to people aged <20 years who need to catch up on vaccination.

## Other recommendations for vaccination

### People who are immunocompromised

People who are immunocompromised have a higher risk of persistent HPV infection and related disease. The conditions where the three-dose schedule is required include primary or secondary immunodeficiencies (B lymphocyte antibody and T lymphocyte complete or partial deficiencies), HIV infection, malignancy, organ transplantation or significant immunosuppressive therapy.

### Men who have sex with men

Men who have sex with men are recommended to receive HPV vaccination because of their increased risk of HPV infection and associated disease, notably genital warts and anal cancer.[18] They are also less likely to benefit from herd protection attained from HPV vaccination of females.

### Women treated for high-grade cervical disease

HPV vaccination should be considered for women who have received treatment for cervical intraepithelial neoplasia (CIN) 2+ (i.e. high-grade cervical disease) to reduce future susceptibility to HPV-related disease. The vaccine will have no impact on current infection or disease but can prevent reinfection (e.g. from a partner), spread of infection through the genital tract and new infection with other HPV types covered by the vaccine.[19]

### Adults aged ≥19 years

Vaccination of all adults aged 19 years and older is not routinely recommended, as the benefits of vaccination are lower in those already exposed to vaccine HPV types through sexual activity.

A recent study estimated that of all the HPV infections that cause cervical cancer, 50% have been acquired by age 20 and 75% by the age of 30.[20] Thus the capacity to benefit from HPV immunisation decreases with increasing age. Cervical cancer prevention in sexually active women (whether vaccinated or not) is best achieved through cervical screening.[9]

# Vaccines

All HPV vaccines contain virus-like particles (VLPs) which are made using recombinant vaccine technology. They are not live vaccines. HPV vaccines are not therapeutic vaccines and will not clear an existing HPV infection. HPV vaccines elicit antibody titres many times higher than those observed in natural infection.[21-25]

### 9-valent HPV vaccine

Gardasil9 (Seqirus/Merck & Co Inc) is a 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) registered in Australia for use in females aged 9–45 years and males aged 9–26 years. Gardasil9 is the HPV vaccine used in Australia's National HPV Vaccination Program.

### Quadrivalent HPV vaccine

Gardasil (Seqirus/Merck & Co Inc) is a quadrivalent VLP HPV vaccine (4vHPV; types 16, 18, 6 and 11) registered in Australia for use in females aged 9–45 years and in males aged 9–26 years. Gardasil was used in the National HPV Vaccination Program from 2007 to 2017, but has been replaced by Gardasil9 since 2018.

### Bivalent HPV vaccine

Cervarix (GlaxoSmithKline) is a bivalent VLP HPV vaccine (2vHPV; types 16 and 18) registered in Australia for use in females aged 10–45 years. Cervarix is not registered for use in males of any age. It is supplied in Australia only on the private market.

## Dose and route

The dose of 9vHPV, 4vHPV and 2vHPV vaccine is 0.5 mL administered intramuscularly.

A two-dose schedule is recommended for those who receive their first HPV vaccine dose before their 15th birthday, administered at 0 (the day the first dose is given) and 6–12 months. If an individual has received two doses of HPV vaccine with an interval of <5 months between dose 1 and dose 2, then a third dose is needed at least 12 weeks after the second dose.

A three-dose schedule is recommended for anyone who is immunocompromised (any age) and those who receive their first HPV vaccine dose on or after their 15th birthday, administered at 0, 1 and 6 months for 2vHPV vaccine, and at 0, 2 and 6 months for 9vHPV and 4vHPV vaccines. Older adolescents (who are not immunocompromised) who commence vaccination after turning 15 years may need to pay to complete the schedule, as only two doses are funded.

The minimum acceptable interval for HPV vaccines in a three-dose schedule is 4 weeks between doses 1 and 2, and 12 weeks between doses 2 and 3. A minimum interval of 5 months is required between dose 1 and dose 3.

If scheduled doses have been missed, earlier doses should not be repeated. The missed dose(s) should be given as soon as practicable.

Re-vaccination with the 9vHPV vaccine is not routinely recommended for those who have previously completed an HPV vaccination schedule with either 4vHPV or 2vHPV vaccine.

The World Health Organization recently recommended that HPV vaccine can be used in a one-dose schedule for people aged 9 to <20 years and in a two-dose schedule for people aged ≥21 years.[26] However, the vaccination schedule remains unchanged in Australia.

Pre-immunisation screening with HPV tests or by serological testing is not warranted.

## Vaccine efficacy/effectiveness

The efficacy of HPV vaccines has been extensively assessed in clinical trials enrolling females. In women who are naïve to (i.e. have never been infected with) the vaccine HPV types, 9vHPV vaccine is highly effective (>96%) in preventing persistent-type specific infection and high-grade cervical, vulvar and vaginal disease associated with these HPV types.[27] Younger adolescents, both female and male, aged 9–14 years develop higher levels of HPV antibodies than older adolescents and young women in whom clinical efficacy has been demonstrated.[24,25,28]Similarly, 4vHPV and 2vHPV vaccines are highly efficacious and immunogenic against their respective HPV types.[21,23-25,29-34]

HPV vaccination has been hugely successful in reducing rates of HPV-associated disease in Australia.[35] Since the HPV vaccination program began in 2007, rates of genital warts have declined by more than 90% in younger vaccinated populations.[36] The incidence of high-grade cervical abnormalities has decreased in women up to 30 years of age.[13,37,38] High rates of HPV vaccination have resulted in declines in the prevalence of 4vHPV types among Aboriginal and Torres Strait Islander women by up to 94%.[39] These declines are expected to translate into declines in cervical cancer in the coming years and can reduce disparities in cervical cancer incidence among Aboriginal and Torres Strait Islander and non-Indigenous women. Australia is currently working towards achieving the elimination of cervical cancer by 2035; however, with continued high rates of vaccination and cervical screening, this could happen by 2028.[40,41]

Among men, HPV vaccination prevented more than 85% of persistent anogenital infections and external genital lesions due to 4vHPV types among HPV-naïve participants. Among participants who were men who have sex with men, vaccine efficacy was 95% against intra-anal HPV

infection and 75% against high grade anal intraepithelial neoplasia from vaccine HPV types. A recent study of men who have sex with men in Victoria found that up to 29% of new HPV infections could have been prevented through vaccination with 9vHPV vaccine.[42]

Duration of immunity through vaccination is likely to be long-term, with stable antibody titres demonstrated for over 10 years after immunisation with 2vHPV and 4vHPV vaccines and up to 8 years with 9vHPV vaccine.[27,43-45 46] Pre-adolescent males and females have a good immune response to vaccination, producing higher antibody levels than young women.[24,47,48]

## Vaccine safety

HPV vaccines are included in national immunisation schedules in 107 countries,[49,50] with more than 270 million doses distributed worldwide.[51] Extensive data from clinical trial and post-marketing safety surveillance indicate that the 9vHPV, 4vHPV and 2vHPV vaccines are well tolerated and safe.[52-54]

The main side effects of the vaccines are local reactions at the injection site (pain, redness and swelling). These reactions occur in about 80–90% of vaccine recipients but are less frequent in younger girls and in boys than in adult women.[47,55,56] Syncope (fainting) is one of the more commonly reported adverse events that was reported when HPV vaccine was first introduced (reported at a rate of 29.6 per 100,000), but is now very rarely reported (7.1 per 100,000 doses[57]). The 9vHPV vaccine has demonstrated a similar safety profile to that of the 4vHPV vaccine, but with a slightly increased frequency in injection site reactions, likely due to the increased concentration of adjuvant.[52,58] Data from multiple clinical trials and post-marketing use show that the 9vHPV, 4vHPV and 2vHPV vaccines do not increase the risk of serious adverse events (SAEs) among vaccine recipients compared with control/placebo recipients.[56,58-61]

There is no strong scientific or epidemiological evidence to suggest that HPV vaccines can induce syndromes such as premature ovarian failure (POF), postural tachycardia syndrome (POTS) or complex regional pain syndrome (CRPS).[62] These diseases of unclear aetiology unfortunately occur in adolescents and young people, whether they are vaccinated or unvaccinated, and there is no evidence that these conditions occur more frequently in HPV-vaccinated populations. There is also no evidence that HPV vaccination is linked to infertility.[63,64] The Global Advisory Committee on Vaccine Safety of the World Health Organization has reviewed HPV vaccines nine times – most recently in 2019 – and continues to endorse their safety and use in young adolescents.[64]

## Concomitant administration with other vaccines

9vHPV vaccine has been assessed in clinical trials when delivered concomitantly (at the same visit but at a separate injection site with a separate syringe) with reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTpa) and quadrivalent meningococcal (A, C, $W_{135}$, Y) conjugate vaccine (4vMenCV).[65,66] Co-administration was well tolerated and induced a robust immune response to all vaccines. HPV vaccine can be co-administered with COVID-19 vaccines.[67]

## Interchangeability

9vHPV vaccine can be used to complete an HPV vaccination schedule commenced with either 4vHPV vaccine or 2vHPV vaccine. Previously administered doses do not need to be repeated (if given at the appropriate interval), regardless of the time since those doses were administered.

### Contraindications/precautions

HPV vaccine should not be given to anyone who has experienced an anaphylactic reaction after a previous dose of the vaccine or to any component of the respective vaccine (including yeast for 9vHPV and 4vHPV vaccines).

HPV vaccine should not be administered during pregnancy. If an HPV vaccine is inadvertently administered during pregnancy, the rest of the vaccination schedule should be deferred until after pregnancy. Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed that the scientific evidence suggests there is no harm to the pregnant woman or her foetus. For more information on vaccine safety during pregnancy, refer to the Australian Immunisation Handbook.

## Other considerations

### Cervical screening in women who have been vaccinated

Regular cervical screening tests are still recommended, as per national guidelines under the renewed National Cervical Screening Program, for women who have received HPV vaccine. Screening for women aged 25–74 years is recommended every 5 years (or 2 years after the last Pap test). In sexually active women, the most important preventive intervention against cervical disease remains regular cervical screening. Vaccination is *not* an 'alternative' to cervical screening; together these two approaches provide optimal protection against disease.

More information about the National Cervical Screening Program can be found at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1.

### Responding to questions about HPV vaccine

Please see the NCIRS fact sheet HPV vaccines – frequently asked questions for information to assist providers in answering patient concerns about the vaccine.

## Additional resources for primary medical care/vaccination providers

- The Australian Immunisation Handbook
- Immunisation Australia website

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